Methotrexate Chemotherapy Induces Persistent Tri-glial Dysregulation that Underlies Chemotherapy-Related Cognitive Impairment.

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Public Summary:
Chemotherapy results in a frequent yet poorly understood syndrome of long-term neurological deficits. Neural precursor cell dysfunction and white matter dysfunction are thought to contribute to this debilitating syndrome. Here, we demonstrate persistent depletion of oligodendrocyte lineage cells in humans who received chemotherapy. Developing a mouse model of methotrexate chemotherapy-induced neurological dysfunction, we find a similar depletion of white matter OPCs, increased but incomplete OPC differentiation, and a persistent deficit in myelination. OPCs from chemotherapy-naive mice similarly exhibit increased differentiation when transplanted into the microenvironment of previously methotrexate-exposed brains, indicating an underlying microenvironmental perturbation. Methotrexate results in persistent activation of microglia and subsequent astrocyte activation that is dependent on inflammatory microglia. Microglial depletion normalizes oligodendroglial lineage dynamics, myelin microstructure, and cognitive behavior after methotrexate chemotherapy. These findings indicate that methotrexate chemotherapy exposure is associated with persistent tri-glial dysregulation and identify inflammatory microglia as a therapeutic target to abrogate chemotherapy-related cognitive impairment.

Scientific Abstract:
Chemotherapy results in a frequent yet poorly understood syndrome of long-term neurological deficits. Neural precursor cell dysfunction and white matter dysfunction are thought to contribute to this debilitating syndrome. Here, we demonstrate persistent depletion of oligodendrocyte lineage cells in humans who received chemotherapy. Developing a mouse model of methotrexate chemotherapy-induced neurological dysfunction, we find a similar depletion of white matter OPCs, increased but incomplete OPC differentiation, and a persistent deficit in myelination. OPCs from chemotherapy-naive mice similarly exhibit increased differentiation when transplanted into the microenvironment of previously methotrexate-exposed brains, indicating an underlying microenvironmental perturbation. Methotrexate results in persistent activation of microglia and subsequent astrocyte activation that is dependent on inflammatory microglia. Microglial depletion normalizes oligodendroglial lineage dynamics, myelin microstructure, and cognitive behavior after methotrexate chemotherapy. These findings indicate that methotrexate chemotherapy exposure is associated with persistent tri-glial dysregulation and identify inflammatory microglia as a therapeutic target to abrogate chemotherapy-related cognitive impairment. VIDEO ABSTRACT.

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